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FDA Guidance for Abuse-Deterrent Opioids: Is there an Opportunity for a Label Change?

31January 2013

US Medical Affairs

FDA Draft Guidance on ADF

Meeting Objective is to align on:

- What it is
  - Overview of the Guidance
- What it means for TAP
  - Brief overview of pertinent data
  - Questions to FDA
- What we do about it
  - Request to meet with FDA?
  - Immediately pursue Tier 1 or Tier 2 claim?
  - How about Tier 3 or 4 claim?

Agenda

Topic	Presenter	Time
Objectives and open remarks	M. Kim	10
Overview of the FDA guidance for abuse deterrent formulations	G. Vorsanger/H. Rofael	30 min
Available TAP Data • Molecule level abuse studies: •Preclinical PK/Tox studies; •Likability study •studies on TRF 2.Lab data ; 3.PK studies; 4.Columbia University studies ; 5.Chewing study ; 6.RADARS and Inflexxion.	10 min for the presentation •G. Eichenbaum •P. Zannikos •Y. Williams •P. Zannikos •D. Shapiro •B. McCann, •G. Vorsanger	70 min
Break		10 min
Discuss proposed questions to the FDA	G. Vorsanger/	15 min
Discuss the options moving forward	team	45 min

Overview of the FDA Guidance on Abuse-Deterrent Opioids

Overview by

Gary Vorsanger

FDA Guidance
Abuse Deterrent Opioids

Background

- Intended to assist sponsors who wish to develop formulations of opioid drug products with potentially abuse-deterrent properties
- Guidance explains FDA's current thinking
- The science of abuse deterrence is relatively new
- FDA will take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products.
- FDA welcomes comments and suggestions on this guidance

FDA Guidance
Abuse Deterrent Opioids

III. OPIOID ABUSE-DETERRENT FORMULATIONS

As a general framework, abuse-deterrent formulations can be categorized as follows:

- Physical/Chemical barriers – Physical barriers can prevent chewing, crushing, cutting, grating, or grinding. Chemical barriers can resist extraction of the opioid using common solvents like water, alcohol, or other organic solvents
- Agonist/Antagonist combinations – An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse
- Aversion – Substances can be combined to produce an unpleasant effect if the dosage form is manipulated prior to ingestion or a higher dosage than directed is used
- Delivery System (including depot injectable formulations and implants) – Certain drug release designs or the method of drug delivery can offer resistance to abuse., sustained-release depot injectable formulation that is administered intramuscularly or a subcutaneous implant can be more difficult to manipulate
- Prodrug – A prodrug that lacks opioid activity until transformed in the gastrointestinal tract can be unattractive for intravenous injection or intranasal routes of abuse.
- Combination – Two or more of the above methods can be combined to deter abuse.

FDA Guidance
Abuse Deterrent Opioids

IV. PREMARKETING STUDIES

In order to obtain a full and scientifically rigorous understanding of the impact of a technology or technologies on a product's abuse potential, data from each of the following three categories of premarketing studies are appropriate:

1. Laboratory-based in vitro manipulation and extraction studies (Category 1)
2. Pharmacokinetic studies (Category 2)
3. Clinical abuse potential studies (Category 3)

- The results of Category 1 studies influence the design of Category 2 pharmacokinetic studies, and the results of Category 2 studies influence the need for Category 3 studies of human abuse potential and the designs and goals of these studies. Category 4 studies analyze post marketing data to assess the impact of an abuse-deterrent formulation on actual abuse.

FDA Guidance
Abuse Deterrent Opioids

PREMARKETING STUDIES

A. **Laboratory Manipulation and Extraction Studies (Category 1)**

- Designed to evaluate the ease with which the formulation can be defeated or compromised
- *Comment:* These are the type of studies that were addressed in evaluating GRT/INTAC technology

B. **Pharmacokinetic Studies (Category 2)**

- Needed to evaluate the *in vivo* properties of the formulation by (a) comparing the pharmacokinetic profiles of the manipulated formulation with the intact formulation and (b)with manipulated and intact formulations of the comparator drugs through one or more routes of administration
- *Comment:* Data would be in Nucynta ER NDA and discuss with GRT/INTAC

C. **Clinical Abuse Potential Studies (Category 3)**

- *The preferred design is a randomized, double-blind, placebo-controlled and positive comparator controlled crossover study*. These studies generally are conducted in a drug-experienced abuser population
- *Comment:* See labeling section re: requirement for all 3 categories

FDA Guidance
Abuse Deterrent Opioids

V.POSTMARKETING STUDIES (Category 4)

- Should be designed to determine whether marketing of the abuse-deterrent formulation results in a significant decrease in population-based and use-based estimates of abuse compared to estimates of abuse of formulations without these properties

- FDA acknowledges that the optimal design features of these type of post marketing epidemiologic studies have not yet been established

- Requirement: need to be capable of detecting a change in the occurrence of abuse and abuse-related clinical outcomes (addiction, overdoses, poisonings, and death) as a result of the drug product's abuse-deterrent formulation
- *Comment-Unlike OxyContin or Opana where a reduction in abuse could be documented when TRF was introduced, Nucynta ER has always had a TRF*

FDA Guidance
Abuse Deterrent Opioids

VI. LABELING

- There are four general tiers of claims available to describe the potential abuse-deterrent properties of a product
- These tiers generally correlate with the four categories-premarketing and post marketing described above

  Tier 1: The Product is Formulated with Physicochemical Barriers to Abuse

  Tier 2: The Product is Expected to Reduce or Block Effect of the Opioid When the Product is Manipulated

  Tier 3: The Product is Expected to Result in a Meaningful Reduction in Abuse

  Tier 4: The Product has Demonstrated Reduced Abuse in the Community

- Draft guidance indicates that FDA generally expects sponsors to provide data from Categories 1, 2, *and 3 in order to be* eligible for Tier 1, Tier 2, or Tier 3 claims
  - **E.g., Category 1 data alone likely will not be sufficient to support a Tier 1 claim; Category 2 or 3 data (or both) may be needed to ensure that a Tier 1 claim is not misleading**

Tier 1: Claims that a Product is Formulated with Physicochemical Barriers to Abuse

- The specific properties that resist manipulation and/or that result in the release of components of the formulation that may limit its ability to be abused should be described. In addition, the specific route or routes of administration affected by these abuse deterrence properties should be described.

- **An example of a Tier 1 claim could be:**
  - *These data demonstrate that, when the intact formulation is ground in a coffee grinder, the resulting particle size makes insufflation extremely difficult; and when those particles are heated they form a gelatinous substance that cannot be drawn up into a syringe or insufflated. Therefore, it appears that injection or snorting of the manipulated drug product would be difficult. However, abuse of this product is still possible by the oral route.*

- This statement would be followed by an appropriate acknowledgment that data from laboratory studies may not fully predict real-world abuse potential, that post-marketing studies are ongoing, and that this information may be modified based on the results of such studies**.**

Tier 2: Claims that a Product is Expected to Reduce or Block the Effect of the Opioid When the Product is Manipulated.

- Pharmacokinetic data may also be used to demonstrate a product's abuse deterrence.

- **An example of a Tier 2 claim could be:**
  - *These data demonstrate that, when the intact product is heated in a solvent suitable for injection and the resulting solution is injected, the opioid antagonist component is released into the systemic circulation at a pharmacokinetic exposure level that may result in blocking of the opioid's agonist effects, or in a mild to moderate degree of opioid withdrawal in an opioid-tolerant individual. However, abuse of this product is still possible by the oral route.*

- This statement would be followed by an appropriate acknowledgment that data from laboratory and clinical studies may not fully predict real-world abuse potential, that post-marketing studies are ongoing, and this information may be modified based on the results of such studies.

Tier 3: Claims that a Product is Expected to Result in a Meaningful Reduction in Abuse.

- The Agency believes that reductions in drug "liking" generally are likely to result in meaningful reductions in abuse. However, data from Category 1 and 2 studies should serve as the basis for performing the Category 3 studies and will provide important supportive information in understanding the results of a Category 3 study.

- If data from Category 3 studies are robust, Tier 3 labeling claims and data regarding the design, conduct, and data from Category 3 studies may be included in the product labeling.

- **An example of a Tier 3 claim could be:**
  - *These data demonstrate that the inclusion of the opioid antagonist component in the product's formulation results in a decrease in euphoria and "liking" when a solution of the product in a suitable solvent for injection has been heated and the resulting solution injected parenterally. Based on these findings, this product's specific formulation may result in reduced abuse by parenteral injection. However, abuse of this product is still possible, including by the oral route or by snorting when the product is crushed.*

- This statement would be followed by an appropriate acknowledgment that data from laboratory and clinical studies may not fully predict real-world abuse potential, that post-marketing studies are ongoing, and this information may be modified based on the results of such studies.

Tier 4 claim: The Product has Demonstrated Reduced Abuse in the Community

- FDA anticipates that data from Category 1, 2, 3, and 4 studies (including both formal studies and supporting data) would be needed to support a Tier 4 claim.

- The combined results from all of these studies would be described in the product labeling, including specific study designs, conduct, analyses, and study data.

- **An example of a Tier 4 claim could be:**
  - *These data have demonstrated a reduction in abuse of this opioid in the community setting compared to the levels of abuse, overdoses, and deaths that occurred when only formulations of the same opioid without abuse deterrence properties were available.*
  - *This reduction in abuse appears to be due to the product's particular formulation, which deters parenteral injection and snorting of the manipulated product. However, such abuse of this product is still possible, and the product's abuse deterrence properties do not deter abuse associated with swallowing the intact formulation.*
- This statement would be followed by an appropriate acknowledgment, if applicable, that postmarketing studies are ongoing and that this information may be modified based on the results of those studies

Molecule Level Abuse Studies

Tapentadol – Nonclinical Abuse Liability Assessment-Summary

Gary Eichenbaum

- The studies that were conducted fall into the following categories:
  - self-administration (reinforcing behavior),
  - conditioned place preference (self-administration) drug discrimination (compound class – e.g. opioids),
  - physical dependence (withdrawal signs), and
  - tolerance (reduction in efficacy with repeat dosing).

- Nonclinical data from studies in mice, rats and monkeys demonstrate that Tapentadol exhibits opiate-like effects with respect to reinforcing behavior but shows less physical dependence and tolerance development compared to morphine .

- Despite the results supporting improved physical dependence and tolerance development , the DEA concluded that Tapentadol should be treated in the same way as other Schedule II Opioids such as Morphine.

- DEA appeared to make this conclusion based on the conditioned place preference and monkey self-administration study results and did not discuss the reduced evidence of physical dependence in the mouse or rat withdrawal tests or appear to factor in the reduced tolerance in making their conclusion regarding the overall abuse potential of Tapentadol.

Likability study

Peter Zannikos

Abuse Potential of Tapentadol Immediate-Release (IR)

Study PAI-1007/HP14

Objective

To evaluate the abuse potential of tapentadol IR as compared to placebo and hydromorphone IR

Design

Single-center, single-dose, double-blind, double-dummy, placebo-controlled, randomized, 7-way cross-over

Subjects

Opiate-experienced but non-dependent recreational drug users

Abuse Potential of Tapentadol Immediate-Release (IR) (cont)

Single Oral Dose Treatments:

- Tapentadol IR: 50, 100, and 200 mg
- Hydromorphone IR: 4, 8, or 16 mg
- Placebo

Pharmacodynamic Endpoints:

- Overall Drug Liking (primary endpoint)
- Subjective Drug Value
- Subjective Effects
- Observer-rated single-dose questionnaire
- Subject-rated Opiate Agonist Scale
- Addiction Research Center Inventory
- Divided attention test
- Choice reaction time test

Abuse Potential of Tapentadol Immediate-Release (IR) (cont)

Key Pharmacodynamic Results:

- The highest dose of hydromorphone IR was differentiated from placebo for the primary endpoint, confirming the validity of the results of the study.

- There were no statistically significant differences for the primary endpoint between each calculated equianalgesic dose of tapentadol IR and hydromorphone IR.

- Results for the secondary endpoints were consistent with the findings for the primary endpoint. Tapentadol IR showed similar subjective effects to calculated equianalgesic doses of hydromorphone IR.

Studies on TRF

Tapentadol Tamper Resistant Formulation (TRF): Lab Characterization Tests

Yinka Williams

Categories of in vitro testing

In vitro tests simulated:

- Accidental misuse
- Tampering by Recreational abusers
- Tampering by Experienced abusers
- Tampering by “Kitchen Chemist”

Summary of Recreational Abuse Simulations

- **Chewing simulation**
  - Resulted in about 10% higher release than intact tablet
  - Pre-soaking tablet in artificial saliva for 10 minutes before starting the chewing test did not alter the results
- **Hammered tablet**
  - Resulted in about 10% higher release than intact tablet
- **Frozen (-20C) and hammered tablet**
  - Results similar to non-frozen tablet

- **Automated cutting test**
  - Oxygesic required an average of 3 strokes to cut through tablet. TRF required an average of 47-78 strokes
- **“Extraction” of intact tablet and “ingestion” of extract**
  - Intense non-stop shaking for 15 minutes in simulated beverages, followed by dissolution test to simulate ingestion, did not increase release rate

Summary of Simulation of Accidental Misuse

- TRF could not be crushed between two spoons, while Oxygesic™ (EU brand of OxyContin) was easily crushed

- Professional pill crusher: TRF was slightly deformed but not crushed - no change in dissolution curve (i.e., extended release properties retained)

- Breaking Force Tester - At a force of 1000N, TRF tablets were deformed but not broken (Note: Maximum human bite force is 400-600N)

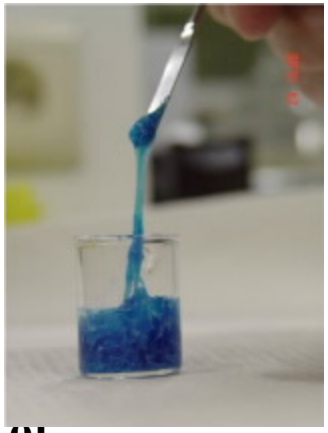
- Intake of intact tablet with alcohol - dissolution rate of a tablet in dissolution medium containing 40% ethanol did not increase.

Summary of Recreational Abuse Simulations (contd)

- **"Extraction" of hammered tablet and "ingestion"**
  - Intense non-stop shaking of hammered for 15 minutes, followed by dissolution test to simulate "swallowing," accelerated the release rate but the tablet still retained some of its extended release properties

Summary of Experienced Abuse Simulations

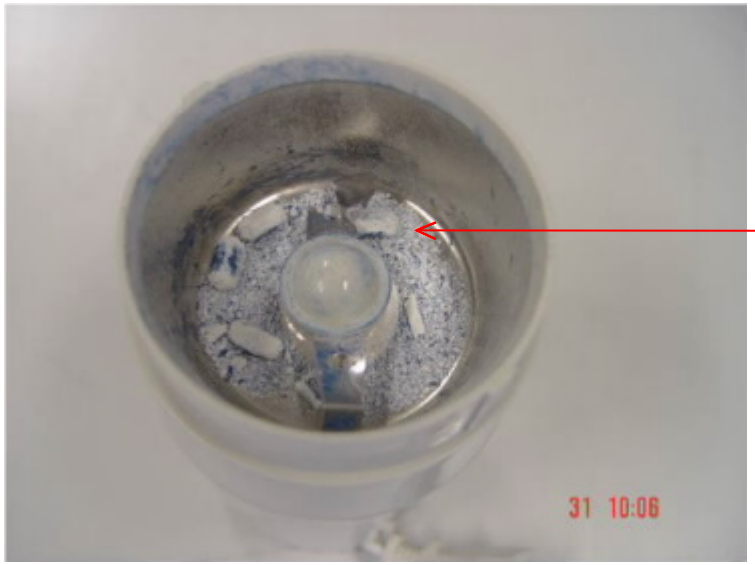
- **"Snorting"**
  - TRF was difficult to pulverize. Therefore, "snorting" will be difficult
- **Smoking**
  - The active ingredient decomposed when heated to the point of vaporization. Therefore, smoking it is unlikely to produce the euphoria expected
- **IV Injection**
  - Dissolution in a small volume of hot water and filtration yielded only about 26% of the tablet content
  - TRF formed a highly viscous uninjectable gel when ground into smaller (but still fairly large) particles and boiled in water.



- **Extraction of intact tablet at high temperatures followed by ingestion of "extract"**
  - 40% of tablet content initially released, followed by slower release

Summary of "Kitchen Chemist" Simulations

- **Coffee grinder**
  - Reduced particle size but the resulting particles were large. "Snortability" of the resulting "powder" is questionable
  - Some brands of coffee grinder broke more easily (e.g., after 5-11 cycles) than others . Given the cost of replacing broken grinders along with the inability of even the best performing brand to pulverize a TRF tablet, it is not anticipated that this will become a method of choice for a significant number of abusers.



Broken blade of coffee grinder

Summary of "Kitchen Chemist" Simulations

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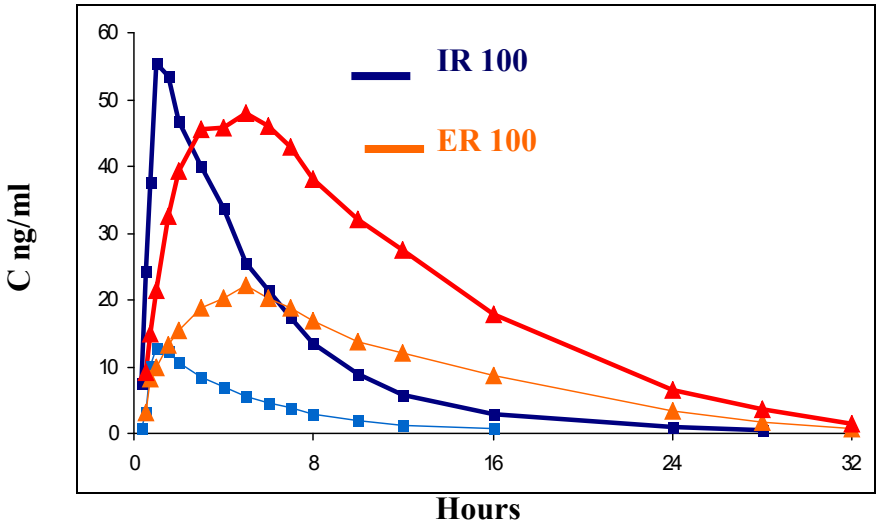
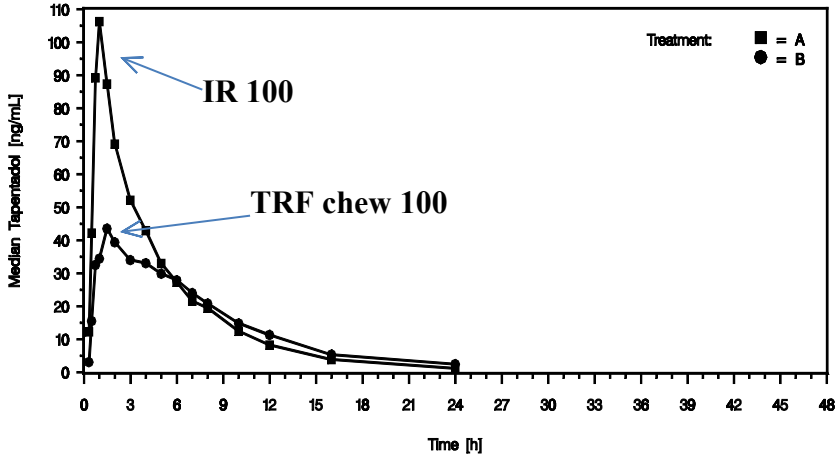
- **Extraction of intact tablet with solvents**
  - Methanol was the most effective extraction solvent but using it is dangerous and requires further steps to get at the active ingredient
- **Extraction of ground or hammered tablet at room temperature**
  - Ground or hammered tablets yielded most of the drug in 15-60 minutes when intensely shaken/extracted with room-temperature solvents
  - Ground or hammered tablets yielded most of the drug in 5 minutes when intensely shaken/extracted with solvents at boiling point

R331333 PAI 1047
Chew Study

Bettyanne McCann

PK Results: Ph1 vs Chewed Values

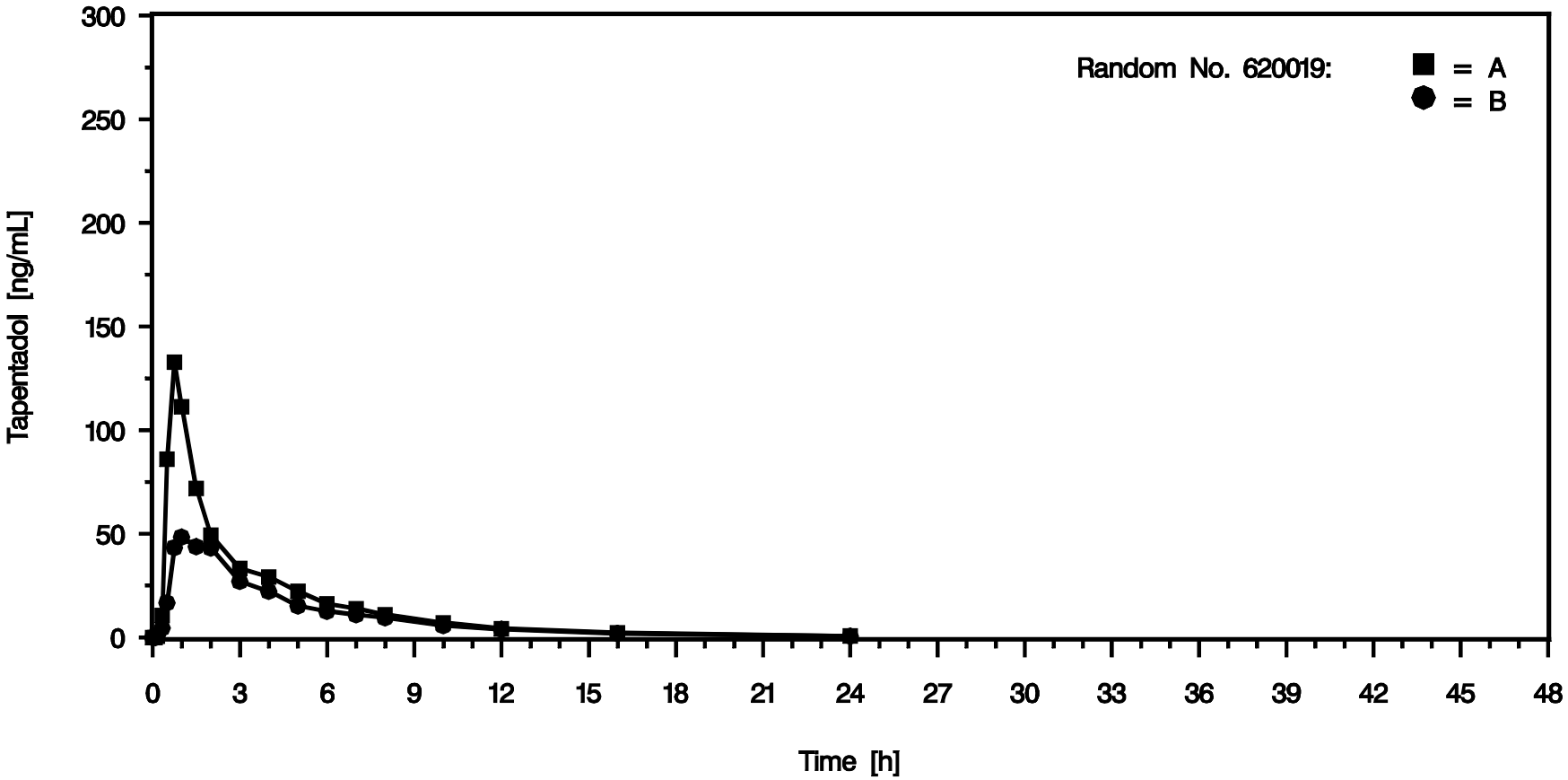




	IR whole	TRF chewed	TRF whole
T_{max} (h)	1h	1.5h	1.4
C_{max} (ng/mL)	129 ng/ml	55.8 ng/ml	35 ng/ml
$T_{½}$ (h)	4.78h	4.99h	3.6h
AUC_{inf} (h.ng/mL)	462	424	465

Cmax Variability

Subject # 620019 (small adherent pieces, 22 min)



IR: 132.9 ng/ mL TRF: 48.5 ng/mL A=IR B=TRF

Objectives/Design/PK/Safety/Summary

Objective - Evaluation/comparison of safety, tolerability and PK

- Tapentadol IR 100mg **whole**/ TRF 100mg **chewed**/then swallowed
- The majority of subjects following the masticated TRF tablet compared with the IR tablet.
- ER characteristics were maintained in ***19 of 24*** subjects despite extensive chewing of TRF for ***3 minutes***.
- ***5 of 24*** profiles suggest tapentadol pK after chewing reflects a contribution of both IR and ER properties.
- No changes to dentition or oral cavity after chewing TRF.
- No clinically meaningful changes – labs, vital signs, or ECG
- More TEAEs in IR than TRF 83% vs 62%
- The safety profile of tapentadol remained the same as previous studies.

Effect of Concomitant Food & Ethanol Intake

Peter Zannikos

Concomitant food intake

- No significant effect on the AUC of tapentadol was observed when tapentadol TRF or PR2 250-mg tablets were administered after a high -fat, high-calorie breakfast.

- A small increase of 17% to 18% in C_{max} was observed when administered with food, but was judged to be of no clinical relevance

Concomitant Ethanol Intake

- Co-administration of alcohol led to an initially faster increase in tapentadol concentrations, particularly in the first 1 to 2 hours after drug intake.
- Concomitant intake of alcoholic beverage with tapentadol ER (TRF) 100 mg and 250 mg tablets had only a minimal effect on AUC but did increase C_{max}. Based upon the least squares mean ratios an increase of 48%, 17%, and 17% for C_{max}, $AUC_{last,}$ and AUC_{∞}, respectively, was observed for tapentadol ER 100 mg and of 28%, 16%, and 16% for C_{max}, $AUC_{last,}$ and AUC_{∞}, respectively, for tapentadol ER 250 mg.
- The alcohol effect is most apparent for C_{max} in the 100 mg dose group, where on subject level, C_{max} values increased up to 4.38 times following concomitant administration of 240 mL of 40% alcohol.
- In the 250 mg dose group, C_{max} values increased up to 2.67 times, on subject level, following concomitant administration of 240 mL of 40% alcohol.

Abuser attempts to overcome tapentadol TRF properties

Douglas Y. Shapiro

Design of 2 studies at Columbia Institute of Psychiatry

- **Objective:** whether experienced abusers of OxyContin could prepare tapentadol TRF tablets for intranasal or intravenous abuse
- **Method:**
  - 3 test tablets presented in random order to participants: OxyContin 40 mg, TRF 50 mg, and TRF 250 mg
  - Participants instructed to prepare tablets for intranasal (Study 1) or intravenous (Study 2) use with any tools they requested
  - Preparation time limited to 1 hour per tablet
- **Endpoints:**
  - Intranasal study = % willing to snort tampering output; and particle size analysis
  - Intravenous study = % yield of active drug in solution drawn up into a syringe

Intranasal study results

Intranasal particles

	Particle size & willingness to snort tampering product		
% < 850 µ	79.2 %	2.1 %	1.3 %
# particles (mean)	41,595	1,337	1,808
% willing snort	100 %	24 %	16 %

Conclusion: In comparison with OxyContin 40 mg tablets, TRF tablets could only be rendered as a very small number of particles that were mostly too large to be snorted. Fewer subjects were willing to snort the TRF particles.

Intravenous study results

In small volumes used by abusers, most TRF ended as gelatinous mass not in syringe. Most Oxy ended in syringe.

	Active drug in syringe & willingness to inject syringe contents		
% yield (mean)	37.0 %	3.5 %	0 %
Active drug obtained (mean)	14.8 mg	1.8 mg	0 mg
% willing to inject	100 %	16 %	0 %

Conclusion: Less than 1/10th as much TRF could be dissolved and sucked into syringe as Oxy, with smaller proportion of active drug obtained and many fewer abusers willing to inject the tampered product.

RADARS Publications

Gary Vorsanger

Posters

1. Surratt H et al (CPDD) 2012: Street prices of prescription opioids diverted to the illicit market: data from a national surveillance program.

- **Methods:**
  - Street price data were obtained from 687 questionnaires collected during 7 quarters in 2010 and 2011. Median prices were computed per milligram for the targeted prescription opioids in order to make standardized price comparisons across drug classes. Trends in price data over time were also examined.
- **Results:**
  - Median price/mg of Tapentadol was the lowest among the tested opioids and was $0.1 which may reflect lower desirability/demand among abuser populations.

2. Dart RC et al. Non-medical Use of Tapentadol Immediate Release by College Students. POSTER PRESENTED AT THE AAPM 28TH ANNUAL MEETING, FEBRUARY 23-26, 2012

- **Objective:**
  - **to describe the rates and methods of non-medical use of tapentadol(TAP)immediate release (IR; among college students based on data from the RADARS® System College Survey Program following FDA approval of TAP-IR and its launch in 2009.**
- **Methods:**
  - **The RADARS System College Survey Program is an online questionnaire that collects data from approximately 2,000 self-identified college students throughout the US during fall, spring, and summer terms annually.**
  - **Responses were analyzed for trends in the rate and method of non-medical use of TAP-IR compared with other opioid analgesics from June 2009 through March 2011.**
- **Results:**
  - **The non-medical use of TAP-IR among college students was highest shortly after its introduction to the market in 4Q2009 (0.66 per 1,000 people who filled a prescription), and decreased significantly in the 4 subsequent survey periods ($p \leq 0.001$).**
  - **Similarly, the rate of non-medical use per 100,000 population was highest in 4Q2009 (0.013 per 100,000 population) and decreased, although not significantly, to 0.004 in 1Q2011 ($p = 0.22$).**
  - **The primary method of non-medical use of TAP-IR among college students was oral intact (49.5%), followed by chewing and inhalation.**
- **Conclusions:**
  - **Since launch, the rates of non-medical use of TAP-IR by college students have been low and have decreased over time.**
  - **The initial levels of reported non-medical use may represent a brief period of experimentation after introduction.**
  - **Continued monitoring is warranted.**

Articles

Dart RC et al: Assessment of the abuse of tapentadol immediate release: The first 24 months. *J Opioid Manag*. 2012;8(6):395-402. doi: 10.5055/jom.2012.0139.

- **OBJECTIVE:**
  - to estimate abuse and diversion rates for tapentadol (TAP) immediate release (IR) compared with oxycodone (OXY), hydrocodone (HYD), and tramadol (TRA) during the first 24 months of TAP-IR availability.
- **METHODS:**
  - Quarterly data from the Poison Center, Drug Diversion, Opioid Treatment, and Survey of Key Informants' Patients (SKIP) programs were plotted to visually compare the rates of TAP-IR abuse and diversion with those of other opioid analgesics from July 2009 through June 2011 using both cases/100,000 population and/1,000 unique recipients of dispensed drug (URDD) as denominators.
  - Trends in abuse and diversion rates over time were determined using a linear regression model of rate versus time.
- **RESULTS:**
  - During the 24 months following its introduction, TAP-IR had very low population-based rates of abuse and diversion that were similar to rates for TRA and lower than rates for OXY and HYD.
  - Rates of TAP- IR abuse and diversion based on URDD were variable by program due to changes in market share and had not stabilized as of June 2011.
- **CONCLUSIONS:**
  - Rates of TAP- IR abuse and diversion have been low during the first 24 months after its launch.
  - Continued monitoring of trends in these data is warranted.

Initial Thoughts on Questions for FDA

Per the FDA guidance,

- "Category 1 data alone likely will not be sufficient to support a Tier 1 claim; Category 2 or 3 data (or both) may be needed to ensure that a Tier 1 claim is not misleading". "In some cases, data from all three categories or "tiers" of studies may not be necessary".

- **Based on the lab, PK and post-marketing data provided, do you agree that Nucynta ER labeling can be updated to include language for Tier 1 or 2 claim?**

- Per the guidance doc, "The goal of postmarketing studies, Category 4, is to determine whether the marketing of the potentially abuse-deterrent formulation results in a significant decrease in population-based and use-based estimates of abuse compared to estimates of abuse if only formulations without abuse-deterrent properties are marketed".
- **Since Nucynta ER has always been marketed in the US with a formulation designed to not be altered by crushing, chewing,..etc, please clarify what data would be required for a Tier 4 claim? Would postmarketing AE data along with data from RADARS be sufficient to support a Tier 4 claim for Nucynta ER? If additional data are required, what additional data would be needed to support this level of claim?**